I. Effects of Key Covariables on Overall Therapeutic Cure Rates

The Cochran-Mantel-Haenszel Test was used to identify any covariables affecting the cure rate. There were no effects of oral contraceptive use, disease severity on admission, condom use and intercourse between admission and Return Visit 1, or condom use and intercourse between Return Visits 1 and 2 on the therapeutic cure rates overall, at the 0.10 level of significance.

J. Symptomatic Relief

The cumulative percentages of patients experiencing symptomatic relief (complete relief of itching and burning/irritation) on Days 3 and 7 of treatment appear in Table XV.

Table XV
Study 95-007-P - Symptomatic Relief in Patients Evaluable for Overall Efficacy - N (%)
per Applicant

	Miconazole Nitrate (4%)	MONISTAT® 7 (2% MCN)
Day 3	22/97 (23%)	20/99 (20%)
Day 7	72/97 (74%)	67/99 (68%)

Although more patients in the miconazole nitrate (4%) vaginal cream group experienced symptomatic relief at Day 7, there was no statistically significant difference between treatment groups at either Day 3 or Day 7. Median time to resolution of symptoms was 4 days in both treatment groups.

K. Adverse Experiences: see Dr. Chin's report.

M. Speciations of Cultures

The distribution of species at admission and at return visits (treatment failures) were evaluated. Approximately 89% of admission species were *Candida albicans* and 3% were *Torulopsis glabrata*. Most treatment failures were still due to *Candida albicans* strains.

MO Comment: The microbiology report by Linda Gosey, FDA microbiologist, observed that 148/159 = 93% of her mycologically-evaluable patients had V1 cultures positive for *Candida albicans*. 6/159 = 4% grew *Candida glabrata* at V1. The remaining 3% were due to other species of *Candida*. By her criteria, 19/23 = 83% of mycological failures were due

to *Candida albicans*, and 3/23 = 13% of mycological failures were due to *C. glabrata*. See Dr. Gosey's review for details.

N. Conclusions

Both treatment regimens provided prompt, safe and effective treatment of vulvovaginal candidiasis. Miconazole nitrate (4%) vaginal cream administered for three days was as safe and as efficacious as currently marketed MONISTAT®7 administered for seven days.

V. OVERVIEW OF RESULTS - EFFICACY

Validity rates were slightly higher in Clinical Study Protocol 95-007-P (69% and 70%) than in Clinical Study Protocol 95-005-P (63% and 62%). However, validity rates were comparable between the two treatment groups in both studies (Table XVII).

Table XVII
Validity Rates for Overall Efficacy - Both Studies per Applicant

	Miconazole Nitrate (4%)	MONISTAT®7 (2% MCN)
95-005-P	87/138 (63%)	88/142 (62%)
95-007-P	98/142 (69%)	100/142 (70%)

Reasons for invalidity were similar in both studies and in both treatment groups. Negative or missing admission KOH preparation or BiGGY culture for *Candida* species was the most frequent reason for invalidity, followed by use of prohibited medication, failure to return, and lost to follow-up.

MO Comment: The applicant's use of the term validity is the same as the MO's use of the term evaluability.

Table XIX
Overall Study Discontinuation Rates - Both Studies per Applicant

	Miconazole Nitrate (4%)	MONISTAT®7 (2% MCN)
95-005-P	52/138 (38%)	60/142 (42%)
95-007-P	62/142 (44%)	56/142 (39%)

Treatment failure and screening failure were by far the most frequent reasons for study discontinuation, followed by development of another infection and lost to follow-up in Clinical Study Protocol 95-005-P, and by adverse experience and protocol violation in Clinical Study Protocol 95-007-P.

MO Comment: As noted earlier in this review, the MO considered 61/280 = 22% of the subjects in 005, and 49/284 = 17% in 007 to represent screening failures at V1. Furthermore, the MO considered 24/280 = 9% of the subjects in 005, and 47/284 = 17% in 007 to be non-evaluable because of window violations even using the expanded MO visit windows as outlined. The sponsor identified only 3 subjects in the 2 studies who were non-evaluable because of window violations. All other reasons combined added 51/280 = 18% of the subjects in 005 as non evaluable, and 26/284 = 9% in 007 who were considered non-evaluable.

There were no effects of the covariables oral contraceptive use, disease severity on admission, intercourse and condom use between admission and Return Visit 1, or intercourse and condom use between Return Visits 1 and 2 in either treatment group in either study.

Relief of the symptoms of itching and burning/irritation occurred in about 20% of patients in both treatment groups in both studies at Day 3. However, relief of these symptoms at Day 7 was higher in the miconazole nitrate (4%) vaginal cream group in both studies (78% and 74%) than in the currently marketed MONISTAT®7 (miconazole nitrate 2%) Vaginal Cream group (64% and 68%), but neither of these differences were statistically significant.

Median time to relief of symptoms in both studies was 4 days in both treatment groups.

MO Comment: The MO reviewed the sponsor data concerning the above listed covariables, relief of symptoms, and median time to relief of symptoms and agreed with their conclusions.

VI. OVERVIEW OF RESULTS - SAFETY: see Dr. Chin's review.

VII. **MO Discussion and Summary:**

The Agency recommends that for OTC approval of a drug product for the treatment of vulvovaginal candidiasis, the test medication should demonstrate comparable efficacy to an approved 7-day product. Two well-controlled clinical studies are recommended. This NDA included data from two double-blind, randomized, controlled, multicenter studies involving 280 and 284 patients respectively. New base formulation miconazole nitrate vaginal 4% cream (200 mg per prefilled applicator) used once daily for 3 days was compared to "currently marketed" miconazole nitrate vaginal 2% cream (100 mg per prefilled applicator) administered once daily for 7 days. All MO evaluable patients had symptomatic VVC, a positive or missing KOH slide, and a positive yeast culture (for a recognized pathogen) at the entry visit V1.

In the 95-005-P study, the Applicant had 87/138 (63%) evaluable MCN 4% patients, while the MO had 65/138 (47%). The Applicant had 88/142 (62%) evaluable MCN 2% patients, while the MO had 79/142 (56%). The primary efficacy parameter was the overall therapeutic cure rates at RV2. The Applicant reported 58/87 (67%) efficacy in MCN 4% 3-day treatment patients, while the MO had 45/65 (69%) efficacy. In the 7-

day 2% control arm, the Applicant showed 52/88 (59%) efficacy, and the MO analysis showed 49/79 (62%) efficacy. The Applicant's 95% C.I. for therapeutic efficacy was (-6.7, 21.9), while the MO analysis demonstrated a 95% C.I. of (-9.7, 24.1).

In the 95-007-P study, the Applicant had 98/142 (69%) evaluable MCN 4% patients, while the MO had 78/142 (55%). The Applicant had 100/142 (70%) evaluable MCN 2% patients, while the MO had 84/142 (59%). The primary efficacy parameter was the overall therapeutic cure rates at RV2. The Applicant reported 57/98 (58%) efficacy in MCN 4% 3-day treatment patients, while the MO had 46/78 (59%) overall therapeutic efficacy. In the 7-day 2% control arm, the Applicant showed 63/100 (63%) efficacy, while the MO analysis demonstrated 49/84 (58%) efficacy. The Applicant's 95% C.I. for therapeutic efficacy was (-18.4, 8.7) in the 007 study. To adjust for multiple comparisons, the MO analysis used a 97.3% C.I. (-17.2, 19.6).

All four confidence intervals, from the above two studies, demonstrate that miconazole nitrate 4% cream (200 mg) used for three days was statistically equivalent to the 7-day active control miconazole nitrate 2% cream (100 mg).

The overall clinical and microbiological cure rates, cure rates at Return Visits 1 and 2, relapse rates, and symptomatic relief were the secondary efficacy parameters that were examined in the two studies by the Applicant and their data reviewed by the MO. These parameters demonstrated MCN 4% cream to be statistically comparable to the 7-day control arm miconazole nitrate 2% cream.

Over 90% of the infections were due to *Candida albicans* in the Agency's microbiologically evaluable population when the two studies were combined. Unfortunately, we do not know which species might have been present in the 110/564 = 19.5% of subjects (in both studies) who had vulvovaginal symptoms and clinical findings clearly compatible with VVC, but a negative BiGGY culture at the initial visit V1. Almost all of these subjects also had a positive KOH at the initial visit, so it is of interest that so many of these symptomatic subjects had a negative yeast culture. No specific explanation was offered by the Applicant.

The other microbiology finding of note was the combined failure rates for the two most common *Candida* species isolated in the two studies. A total of 19/127 (15%) and 14/132 (11%) of the *C. albicans* strains failed the 4% and 2% MCN treatment arms respectively. The failure rates for *C. glabrata* infections was 6/7 (86%) and 4/5 (80%) in the 4% and 2% MCN treatment arms, demonstrating the inherent resistance of *C. glabrata* to miconazole nitrate. The number of infections due to all the other pathogenic species was too small to allow a valid analysis.

The safety analysis by Ling Chin, M.D., of adverse reactions (body systems involved, severity, and frequency), other safety parameters, and the worldwide postmarketing experience of miconazole nitrate as a topical, vaginal and systemic antifungal product, concluded that there are no new safety concerns to prevent approval of this product for OTC use.

The vaginal cream is a new, more viscous, base formulation. There already exists an approved miconazole nitrate 200 mg 3-day treatment (MONISTAT®3 Combination Pack), but it is administered as a 200 mg suppository with a different base formulation.

The MO weighed the risk/benefit for approving this drug as it pertains to the widespread use of OTC products for treating VVC, the ability of women to self-diagnose the infection, and the trend towards shorter therapies (7 vs. 3 vs. 1 day). In sum, the MO believes this ratio is favorable to the patient in an OTC environment.

MO Final Recommendation:

Approval of miconazole nitrate cream (4%) for the OTC treatment of women with symptomatic vulvovaginal candidiasis and a history of a previously diagnosed vaginal yeast infection.

Approved dosage and route of administration: 3 consecutive daily doses (in prefilled applicators each containing 200mg of miconazole nitrate cream), preferably before going to bed.

A Phase IV Label Comprehension Study is recommended, and postmarketing surveillance requirements should be carefully monitored.

/S/

Daniel Davis, M.D., M.P.H.
Reviewing Medical Officer

cc: NDA 20-827
HFD-40
HFD-40/KLechter
HFD-560
HFD-560/DivDir/DBowen
HFD-560/DepDir/LKatz
HFD-560/MO/LChin
HFD-560/SIO/CTurner
HFD-590/DepDir/RAlbrecht
HFD-590/MTL/BLeissa 7/10/98
HFD-590/M0/DDavis
HFD-590/MO/JWinfield
HFD-590/Micro/LGosey
HFD-590/Chem/DMatecka
HFD-590/Pharm/PColangelo
HFD-590/Pharm/OMcMaster
HFD-590/Stat/CDixon

Concurrence Only:
HFD-590/DivDir/MGoldberger /S/ 7/10/98

Division of Over-the-Counter Drug Products
Medical Officer Review

Applicant:	Advanced Care Products
NDA No:	20-827
Product:	MONISTAT 3 Vaginal Cream (miconazole nitrate 4.0%)
Submission:	NDA submission dated March 31, 1997
Date Received:	April 1997

Introduction

Advanced Care Products is seeking approval of a higher strength miconazole nitrate vaginal cream 4% (MONISTAT 3 Vaginal Cream) for over-the-counter (OTC) use to treat vulvovaginal candidiasis (VVC) in this application. The active ingredient miconazole nitrate has been approved for vaginal candidiasis since 1974 in the United States, prescription (Rx) and over-the-counter (OTC), in various formulations. Miconazole nitrate has also been available Rx, and OTC, in 94 other countries worldwide.

Pertinent to the OTC approval of MONISTAT 3 Vaginal Cream is whether there is sufficient experience for assessment of risk vs. benefit to OTC consumers with this specific formulation. The specific formulation proposed for MONISTAT 3 Vaginal Cream is a new formulation for which there has been no direct marketing experience anywhere in the world. Previously approved (Rx and OTC) MONISTAT vaginal products (See Table 2 on page 3) were all marketed as the older less viscous formulation. MONISTAT products with the new base cream was launched only in the U.S. in November, 1997. Table 1 summarizes the composition of the 3 comparable formulations. I will defer to the chemistry reviewer, the decision about whether or not these changes in composition are significant enough to warrant further testing or require other information.

Table 1: Chemical Composition of the MONISTAT and TERAZOL Formulations

The 2% cream in the old formulation (MONISTAT 7) has been marketed Rx since approval in 1974 in the U.S. Approval for the new formulation of the 2% cream was granted in March of 1997; however this new formulation has only been marketed in the U.S. since November of 1997. This application for approval of the 4% cream (MONISTAT 3) is for a direct-to-OTC marketing (no Rx experience) of an already approved new base cream with a known active ingredient, miconazole nitrate, at a concentration of 4%.

As stated by the sponsor, the new base cream formulation for MONISTAT vaginal cream was designed to "maintain its viscosity at body temperature, thereby addressing the number one consumer complaint for the currently marketed product, i.e. messiness." This new base cream formulation is very similar to the base cream formulation for TERAZOL. (TERAZOL 7 vaginal cream (Rx) was approved in 12/87, and TERAZOL 3 vaginal cream (Rx) was approved in 2/91.) The differences in formulation between MONISTAT 3 and TERAZOL 3 are listed below:

(1) Absence of Butylated Hydroxyanisole (BHA)in MONISTAT 3 Vaginal Cream -

(2) Addition of Benzoic Acid in MONISTAT 3 Vaginal Cream -

(3) Addition of Potassium Hydroxide in MONISTAT 3 Vaginal Cream -

(4) Use of Surfactant -

Finally, the MONISTAT 3 products used in the clinical trials (95-005-P, 95-007-P, 95-009-P) submitted to this NDA for evaluation were in the new base cream formulation.

Safety Evaluation

I. Worldwide Experience

II. Clinical Trial Experience

I. Worldwide Experience:

A. (i) U.S. Experience with MONISTAT

MONISTAT vaginal cream has been approved for vulvovaginal candidiasis since 1974, in the 100 mg strength for 14-day therapy under Rx conditions. The same vaginal cream product was first switched to OTC status in 1991 as a 7-day product. The external vulvar cream used in the 3 and 7 day combination product is identical to those vaginal cream products that have been marketed OTC since 1993. Table 2 lists the MONISTAT products approved for Rx and OTC use in the U.S.

Table 2: List of MONISTAT Products Approved in the U.S.

Name	Dose Formulation	Dose	Duration	Status	Approval
MONISTAT 7	Vaginal Cream	100mg	14 day	Rx	1/30/74
MONISTAT 7	Vaginal Cream	100mg	7 day	Rx	7/28/77
MONISTAT 7	Vaginal Cream	100 mg	7 day	OTC	2/15/91
MONISTAT 7	Vaginal Suppositories	100 mg	7 day	Rx	3/15/82
MONISTAT 7	Vaginal Suppositories	100 mg	7 day	OTC	2/15/91
MONISTAT 7	Combination Pack: Suppository External Vulvar Cream	100 mg	7 day	OTC	4/26/93
MONISTAT 5	Tampon	100 mg	5 day	Rx	10/27/89
MONISTAT 3	Vaginal Suppositories	200 mg	3 day	Rx	8/15/84
MONISTAT 3	Combination Pack: Suppository External Vulvar Cream	200 mg	3 day	OTC	4/16/96
TERAZOL 7	Vaginal Cream	0.8%	7 day	Rx	12/31/87
TERAZOL 3	Vaginal Cream	1.6%	3 day	Rx	2/21/91

MONISTAT products have been available OTC in the U.S. since 1991. A toll-free 800 number was included in the educational brochure with OTC marketing of both the MONISTAT 7 vaginal cream and MONISTAT 7 vaginal suppositories. Table 3 displays the frequency of side effects reported to the 800 number. These side effects were specifically listed in the labeling of OTC MONISTAT 7 products.

Table 3: Side Effects Reported to the 800 Number in the U.S.

Adverse Experience (%)	1991 N=1869	1992 N=1744	1993 N=1098	1994 N=834	1995 N=781	1996 N=882
Burning	31.4	34.7	42.4	34.7	37.6	29.6
Itching	12.6	10.8	10.5	9.2	13.4	8.6
Fever	1.9	0.5	0.5	0.5	0.3	0.9
Back/Shoulder Pain	3.3	1.3	0.9	1.6	0.5	2.3
Lower Abdominal Pain	8.6	6.0	4.1	4.6	6.4	6.6
Headaches	4.5	2.5	1.9	2.2	2.0	3.1
Hives/Skin Rash	7.1	7.9	7.9	9.2	7.9	6.9

The majority of the reports to the 800 number were vulvovaginal in nature. The sponsor stated that approximately 70% of the reports of burning and itching were reported after one, two, and/or three days of therapy, and may be symptoms of the infection itself. From 1991 to 1996, the total number of events reported via the 800

number has declined, from 1869 in 1991 to 882 in 1996, while the sales volume remained consistent; an average of [redacted] units of these products have been sold annually from 1991 to the present.

Medical Officer's Comments:

There is extensive experience with the use of miconazole nitrate, both as a topical antifungal agent, and a vaginal antifungal agent. In 1993, FDA published the final rule on OTC Topical Antifungal Drug Products which included miconazole nitrate (2%) as an active ingredient that has been generally recognized as safe and effective as an antifungal agent for the OTC treatment of athlete's foot, jock itch, and ringworm. The final rule also allowed for professional labeling of miconazole nitrate products for the treatment of superficial skin infections caused by yeast (Candida albicans).

There is no OTC Monograph for antifungal products for the treatment of VVC. The experience with vaginal antifungal products for OTC treatment of VVC comes from the approval and marketing of these products Rx and OTC. However, the specific formulation of this 3-day MONISTAT vaginal cream (200 mg) under consideration for this NDA has not been marketed anywhere in the world, and only since November of 1997 in the U.S.

Consumer complaints about the use of the OTC vaginal antifungal products (available since 1991) received by the sponsor does provide some assurance that most of the complaints were as expected, based on the pre-market clinical trials. Most of these consumer reports were vulvovaginal in nature, some of which may in fact be due to the condition itself. However, the adverse events reported were listed in the labeling of these products, and it remains unclear if there were other types of adverse experiences which were not reported by the consumers because they were not listed in the product labeling. The listing of specific adverse events on product labeling in itself may also prompt certain consumers to report them, who may otherwise not have done so without such labeling.

It is difficult, however, to interpret the information received via the 800 number. The amount of information available about these consumer reports lack detail; specifically, no other information was presented that would allow for an assessment of seriousness of the adverse experience nor of drug-relatedness.

A. (ii) U.S. Experience with TERAZOL

The sponsor also submitted the postmarketing experience (Rx) of the TERAZOL products. In the U.S., TERAZOL 7 vaginal cream was approved in 1987, TERAZOL 3 suppository in 1988, and TERAZOL 3 vaginal cream in 1991. Over [redacted] units of all 3 TERAZOL vaginal products have been distributed in the U.S. A total of 276 patients reported adverse experiences for all 3 formulations from 1/1/93 to 12/31/96. Sponsor reported the incidence of adverse events as 0.001% for the cream formulations.

Of the 276 patients who reported adverse experiences, a total of 142 patients (51%) reported genital reproductive adverse events.

Medical Officer's Comments:

Since the sponsor is asserting that the new MONISTAT formulation is very similar to the TERAZOL formulation, the postmarketing experience from TERAZOL products may be relevant to this application. The brief description submitted by the sponsor appears to confirm what is generally known about vaginal antifungal products; i.e., that the use of these products are extensive and safe, with the majority of adverse experiences reported occurring in the genital reproductive system. However it is not possible to distinguish between events attributable to the active ingredient terconazole itself or to the base cream, which makes extrapolation of ADEs from TERAZOL products to MONISTAT 3 difficult.

In a memorandum issued by the Reports Evaluation Branch at FDA (2/27/96), some concerns were raised about the use of TERAZOL products (7-day cream, 3-day cream, and 3-day suppositories). One death was reported in a 25 year old female due to toxic epidermal necrolysis after administration of TERAZOL vaginal suppositories and cream for vaginal candidiasis. Fifty three cases were found in the FDA Spontaneous Reporting System (SRS) where a possible temporal relationship between terconazole administration (cream and/or suppositories) and a hypersensitivity reaction could be made.

It is difficult to know the relevance of the TERAZOL information to the specific MONISTAT 4% product under consideration, since one cannot attribute the events solely to the terconazole base cream. Even if the terconazole base cream is principally responsible, it would be difficult to extrapolate such data to the MONISTAT 4% product, since the miconazole new base cream is not exactly the same as the terconazole base cream, and the active ingredients are different. Nevertheless, there is reason to warrant vigilant surveillance of the postmarketing experience of MONISTAT 4% (if approved) for early detection of similar serious ADEs noted here.

B. Worldwide Experience

Miconazole nitrate formulations for the treatment of VVC are available in 94 countries outside of the U.S., while the cream formulation (old) is registered in 79 countries. In 34 countries, the products are available OTC. The countries where miconazole nitrate formulations are available are listed in Table 4 below.

Table 4: Worldwide Availability of Miconazole Nitrate Products

OTC	Rx			
Belgium	Libya	Algeria	Germany	Nigeria	Wh. Russia
Benin Republic	Madagascar	Angola	Ghana	Norway	Zaire
Bolivia	Malawi	Argentina	Greece	Pakistan	Zambia
Cameroun	Malaysia	Australia	Guatemala	Panama	
Canada	Mali	Austria	Guinea	Poland	
Congo	Neth. Antilles	Bahrain	Honduras	Portugal	
Costa Rica	New Zealand	Brazil	Iraq	Qatar	
Denmark	Paraguay	Bulgaria	Ireland	Singapore	
Dominican Rep.	Philippines	Burkina Faso	Israel	South Africa	
France	Saudi Arabia	Burundi	Italy	Sri Lanka	
Gabon	Senegal	Columbia	Japan	Sweden	
Luxembourg	South Korea	Cyrus	Jordan	Switzerland	
Hong Kong	Tunisia	Czechoslovakia	Kenya	Taiwan	
Indonesia	United Arab Em.	Ecuador	Martinique	Tanzania	
Ivory Coast	United Kingdom	Egypt	Mauritania	Thailand	
Jamaica	United States	El Salvador	Mexico	Trinidad & Tob.	
Kuwait	Yemen	Ethiopia	Morocco	Uruguay	
Lebanon	Zimbabwe	Finland	Netherlands	Venezuela	

Miconazole nitrate vaginal formulations available outside of the U.S. include the cream, ovules (hard fat), and capsules (soft gelatin capsule). Miconazole nitrate formulations are available outside the U.S. in dosage strengths of 100 mg, 200 mg, 400 mg and 1200 mg.

The sponsor reported worldwide sales from 1981-1989 (excluding the U.S.) of [redacted] treatments of all regimens of miconazole nitrate vaginal products. The total number of reported adverse events (suspected) was 165 from 110 patients. Serious ADEs in total numbered 17 in 8 patients. Over the same time period, the United Kingdom reported [redacted] treatment sold, with 14 adverse experiences reported. It is estimated that the incidence of adverse experiences is 1 in 160,000, with the incidence of serious adverse experiences being 1 in 1.5 million.

A safety update for the gynecological formulations of miconazole nitrate from August, 1991 to August, 1996 from the [redacted] in Belgium reported that approximately 31 million women were treated with miconazole nitrate containing products (excluding U.S. OTC sales). There were 1454 reports of adverse experiences (including U.S. OTC reports), of which 822 met the CIOMS-II (Council for International Organizations of Medical Sciences) criteria. In this same report, the most common complaint was of local irritation/pain/burning at the site of application. New findings from this report consisted of the interaction with latex (given the inclusion of hard fat in some of the non-U.S. formulations), and abdominal/pelvic cramping associated with drug administration.

Medical Officer's Comments:

Overall, the data provided on worldwide experience is without sufficient detail for a comprehensive evaluation. A list of countries where miconazole nitrate products are available Rx or OTC was provided. However, there is no further specification of which specific formulations are marketed in which countries, over what period of time, or if products were withdrawn in any country for any reason. The safety experience is reported for various time periods, 1981-1989 and 1991-1996, with no explanation for why certain time periods are omitted, and whether the databases used for the two time periods are similar. There is also scant description of what the actual adverse events were. A breakdown of the adverse events by the specific dosage forms, to corroborate that there is not any particular adverse event that is particular to the dosage form under consideration, i.e. the cream formulation would also be useful.

The information from the [redacted] safety update is also confusing since U.S. OTC sales are sometimes included, and other times not. Nonetheless, sponsor has conveyed that there is substantial marketing experience (in terms of number of treatments sold) to date with all regimens of miconazole nitrate formulations worldwide, and that the adverse experience profile appears consistent with what is to be expected from the clinical trial data as per the [redacted] safety update. It should, however, be noted that the number of treatments sold does not really provide the actual number of persons exposed to the product. The new findings of abdominal cramping noted in the [redacted] safety update was incorporated into current U.S. labeling as stated by sponsor in Vol. 1.1 of 1.20 page 02-000023 dated 3/31/1997.

Since this new cream formulation is purported to be quite similar to the TERAZOL cream formulation, it would also be useful to have a summary of the worldwide experience with the TERAZOL 7 and TERAZOL 3 cream products.

II. Clinical Trial Experience

a. Placebo controlled studies with TERAZOL Vaginal Cream
(Amendment to NDA 20-827, November 18, 1997, p. 27-28)

During controlled clinical trials in the U.S., terconazole cream at different concentrations were compared to the terconazole base cream (placebo) and miconazole nitrate cream (original formulation). The treatments were self-administered intravaginally for 3 or 7 consecutive days by patients with VVC. In Study C82-075, a total of 280 women were entered into the study. Terconazole cream at 0.4%, 0.8%, and miconazole nitrate cream at 2% administered for 7 days were tested. In Study F85-080, a total of 403 women were entered into the study. Terconazole cream at 0.8%, 1.6%, and miconazole nitrate cream at 2% administered for 3 days were tested.

Table 5: Percent of patients reporting at least 1 adverse experience

	C82-075	N	F85-080	N
0.4% Terconazole	52.9%	70		
0.8% Terconazole	[illegible]	[illegible]	[illegible]	[illegible]
1.6% Terconazole			50.5%	99
2.0% Miconazole	[illegible]	[illegible]	[illegible]	[illegible]
Placebo (Terconazole base cream)	40.3%	72	59.0%	100
[illegible]		280		403
MO calculations: Difference with 95% CI (2.0% Miconazole - 0.8% Terconazole)	[illegible]		2.9 (-10.7, 16.5)	

C82-075:
17.9% of the patients in the placebo group (Terconazole base cream) reported any genital reproductive adverse experiences. "Only 2 patients reported itching, 1 patient reported burning, and 1 patient reported irritation."

F85-080:
The incidence of genital/reproductive adverse experiences were comparable between the groups. There were no statistical differences between study regimens among patients reporting at least one adverse experience.

Medical Officer's Comments:

The information presented for comparison of adverse experiences (ADE) between the TERAZOL, MONISTAT, and placebo (Terazol vehicle) is limited. The actual adverse events were not described. The one reference to the frequency of genital reproductive ADEs in the placebo group in C82-075 did not report what the frequency of such ADEs were either in the TERAZOL or MONISTAT groups, which dismisses any opportunity for comparisons among the different cream formulations. Indeed, it would have been useful to have for comparison the frequency of ADEs encountered with the placebo terconazole base cream vs. a placebo miconazole base cream. However, the miconazole base cream was not tested in these studies.

According to MO's calculations, the difference in adverse events between 2.0% miconazole (MONISTAT 7) and the 0.8% terconazole (TERAZOL 3) groups in these two studies are not significant. However the only conclusion that may be drawn is that the frequency of adverse events (at least 1 adverse event reported) appear comparable among the formulations that were studied.

b. Comparison of new cream formulation vs. original cream formulation:
(Amendment to NDA 20-827, November 18, 1997, p. 30-31)

The safety of the new base cream was established in an approved supplement (S-043) to NDA 17-450 for the MONISTAT 7 vaginal cream. In Study P92-006 MIN), miconazole nitrate 2% in the new base cream (which is a modified TERAZOL base cream), was compared to the original MONISTAT 7 vaginal cream.

Table 6: Comparison of the New Base Cream to the Original Base Cream

	New Base Cream (NDA 17-150/S-043)	Original Base Cream MONISTAT 7	MO's % Difference (New Base Cream minus Original) 95% C.I.
Adverse Experiences	44% (53/120)	50% (61/123)	-6% (-18.5,6.5)
Genital/Reproductive Adverse Experiences	6.7% (8/120)	10.6% (13/123)	-3.9 (-11.0,3.2)

The sponsor stated that there were "fewer genital/reproductive adverse experiences in the new base cream formulation group compared to those in the original base cream group. By MO's calculations, these percentages are comparable.

c. Phase I drug absorption study 95-009-P

This is an open-label, parallel group study of drug absorption of 3 different formulations of MONISTAT vaginal cream in normal subjects. Drug was administered intravaginally for 7 days for the 7-day products and 3 days for the 3-day product. Plasma samples were obtained at specified times pre and post drug administration. Subjects were randomly assigned to one of 3 groups to receive MONISTAT 3 (new formulation), MONISTAT 7 (new formulation) and MONISTAT 7 (old formulation). There were 14 subjects in each arm, all of whom received a full course of the assigned regimen. Following drug administration, subjects were asked to report the development, severity, and abatement of any adverse experiences. Adverse experiences were also assessed by periodic questioning and examining the subjects. All subjects were followed for 72 hours following final study drug administration. No subjects discontinued the study due to adverse experiences. Adverse experiences are reported in the following Table 7.

Table 7: Adverse Experiences in Study 95-009-P

	MONISTAT 3 (new)		MONISTAT 7 (new)		MONISTAT 7 (old)	
Primary term (≥10% Occurrence)	%	N=14	%	N=14	%	N=14
Pain, Abdominal	0%	0	14%	2	7%	1
Constipation	7%	1	0%	0	14%	2
Cramps, GI	14%	2	14%	2	7%	1
Headache	14%	2	29%	4	14%	2
Dizziness	0%	0	7%	1	14%	2
Urticaria	14%	2	7%	1	7%	1
Any adverse experience	57%	8	64%	9	50%	7

Medical Officer's Comments:

This is a drug absorption study comparing 3 formulations (with small numbers of subjects in each treatment arm, N<15) for which adverse experiences were recorded. Across the board, there were no striking differences among the 3 treatment regimens except for the occurrence of headache in the MONISTAT 7 (new formulation) group.

d. Clinical trials with Miconazole Nitrate 4% vaginal cream

The clinical trials submitted to this NDA were multi-center, double-blind, randomized, controlled, parallel-group, comparative studies of 2 to 3 treatment regimens. The studies were conducted under outpatient conditions; and only those subjects with documented VVC (clinical and microbiological) were included. Clinical confirmation required the presence of at least one of the following signs or symptoms: vulvovaginal itching, vulvovaginal burning/irritation, vulvar erythema, vulvar edema, vulvar excoriation, vaginal erythema, and vaginal edema. Patients were seen on admission, treated for 7 days, with follow-up visits 8-10 days and 30-35 days after completion of treatment (drug or placebo). All medication were self-administered. All safety data described below were extracted from study reports submitted to this NDA. Safety was assessed by review and analysis of adverse experiences reported, study discontinuations, and results of follow-up gynecologic examinations.

Study 95-005-P

Two hundred and eighty female patients with vulvovaginal candidiasis were entered into this study at 17 centers. Patients were randomly assigned in chronological order of enrollment to one of two treatment groups: the currently marketed MONISTAT 7 (M7C), old cream formulation, or miconazole nitrate 4% cream (M3C), new cream formulation. Those in the MONISTAT 7 group were treated with drug for seven consecutive nights. Those in the 4% miconazole nitrate group received drug treatment for three consecutive nights and a placebo for the other 4 days.

Safety was assessed via adverse events reporting, examination of reasons for discontinuation, and any changes noted on gynecologic examination. All patients who received study medication and who provided safety data were included in the safety analysis. A total of 270 women were considered in this safety evaluation; 135 in each treatment group. Three patients (1 M3C and 2 M7C) who did not use study medication, and 7 patients (2 M3C and 5 M7C) who were lost to follow-up with no safety data were excluded from the safety analysis.

Compliance was assessed as 93% (126/135) in the M3C group and 95% (128/135) in the M7C group. Compliance was calculated by review of medication use recorded on patient diary cards, and by collection of unused medication and medication packaging.

Table 8: Summary of Adverse Experiences in Study 95-005-P

	Miconazole Nitrate 4% (new)		MONISTAT 7 (old)	
	%	N=135	%	N=135
Any adverse experience	65%	88	67%	91
D/C drug 2° ADE		2		1
Severity of ADE		N=273 events		N=305 events
Mild	35%	96	36%	110
Moderate	44%	119	46%	141
Severe	21%	58	18%	54
Relationship to Drug		N=273 events		N=305 events
Not related	42%	114	49%	148
Unlikely related	19%	52	22%	68
Possibly related	24%	66	25%	76
Probably related	12%	33	26%	78
Highly probably related	3%	8	16%	45

Sixty-five percent of women in the 4% miconazole nitrate group (M3C) experienced a total of 273 adverse experiences while 67% in the MONISTAT 7 group (M7C) experienced 305 adverse experiences. In the M3C group, 21% of ADEs were considered severe. Among these severe cases, 43/58 were vulvovaginal in nature, such as pain, irritation, burning or pruritus of the female genitalia. In the M7C group, 18% of the ADEs were considered severe. Among these severe cases, 36/54 cases were vulvovaginal in nature. A classification of the relationship of the ADE to the study drug is also summarized in Table 8 above.

Medical Officer's Comments:

The sponsor's tabulation of ADEs in Table 8 above show similarity in number of ADE experiences between the M3C and M7C groups. There are two line items where there appears to be higher frequency of ADEs in the M3C group, i.e. ADEs classified as probably related and highly probably related to drug. Further examination of these adverse events in the databases (MED95005 and 9505DATA) provided by sponsor revealed that the actual descriptions of the ADEs in both treatment groups did not appear to be different. All ADEs were vulvovaginal (VV) in nature (such as VV itching, irritation, or burning) whether they were considered probably related or highly probably related. By MO calculations, the difference in frequency of ADEs that were considered probably related between M3C and M7C is significant. Since each subject could report more than one ADE, when each mention of ADEs were linked to individual patients, the difference (by number of subjects affected) between the M3C and M7C groups were narrowed and statistically insignificant. See Table 9 below.

Table 9: ADEs that are Probably Related or Highly Probably Related to Drug

[redacted]	Miconazole Nitrate 2%		MONISTAT 7		By MCT (M3C/M7C)
By Subject	(N=135 subjects)		(N=135 subjects)		Difference % (95% CI)
Relationship to Drug	%	N	%	N	
Probably related	8.8%	12	4.4%	6	[redacted]
Highly probably related	3.0%	4	1.5%	2	1.5 (-2.0,5.0)
By Event	(N=223 events)		(N=305 events)		[redacted]
Relationship to Drug	%	N	%	N	
Probably related	12%	33	2.6%	8	[redacted]
Highly probably related	3%	8	1.6%	5	1.4 (-1.0,3.8)

Among all severe ADEs, there were 37/58 cases (64%) cases in the M3C group which were noted to be possibly, probably, or highly probably related to the drug. Only one patient, #45003 (vulvovaginal itching) had an outcome coded as ongoing, although, under action required for the ADE, no action was required. All of the other patients with severe ADEs with any likelihood of drug-relatedness recovered from the event. No one in this group was hospitalized. Study drug was discontinued in one patient, #14006 (vulvovaginal itching with study medication) and the patient recovered.

A similar analysis of the patients in the M7C group follows:
Among all severe ADEs noted in the M7C group, 28/54 cases (52%) were thought to be possibly, probably, or highly probably related to the drug. Only one patient, #25002 (vulvovaginal itching and burning) had an outcome coded as ongoing, although, under action required for the ADE, no action was required. All of the other patients with severe ADEs with any likelihood of drug-relatedness recovered from the event. No one in this group was hospitalized. Study drug was discontinued in one patient, #17005 (exacerbation of vulvovaginal itching, irritation, and burning) and the patient recovered.

Table 10: Drug Discontinuations in Study 95-005-P

Study Drug	Patient	Age/ Race	ADE	Severity/ Relation	Action	Outcome	Other Notes
M3C	#14006	47/C	vaginal itching on insertion of study medication	severe/ probable	study drug d/c after 2 days	recovered	also receiving Zovirax
M3C	#18002	35/C	bronchitis	severe/ not related	study drug d/c after 3 days because of antibiotic use	recovered	hx of asthma
M7C	#17005	30/H	exacerbation vulvovaginal irritation, itching and burning	severe/ highly probable	study drug d/c after 2 days	recovered	

A total of 3 patients discontinued study medication. The information for discontinuing drug in these 3 patients are provided in Table 10 above, along with a classification of drug-relatedness. In 2 of these 3 patients, it was thought that the

adverse experience may be related to the study drug, Patient #14006 on M3C, and highly probably related in Patient #17005 on M7C. All 3 patients who discontinued drug recovered from the adverse experiences.

Table 11a: Most Frequently Reported Adverse Experiences by Primary Term (>5%)

Adverse Experiences	Treatment Group			
	Miconazole Nitrate 4% (N=135)		MONISTAT 7 (N=135)	
	N	%	N	%
Pruritus, external female genitalia	37	27%	35	26%
Burning, female genitalia	32	24%	31	23%
Headache	25	19%	28	21%
Irritation, female genitalia	22	16%	20	15%
Discharge, female genitalia	4	3%	9	7%
Congestion, respiratory	4	3%	7	5%

Table 11b: Body Systems with the Highest Incidence of Adverse Experiences (>10%)

	Miconazole Nitrate 4% (new)		MONISTAT 7 (old)	
Body System		N=135		N=135
Genital/reproductive system	47%	63	49%	66
Nervous system	19%	25	22%	30
Gastrointestinal system	12%	16	13%	18
Respiratory system	13%	18	9%	12

The most frequently reported ADEs (>5%) in both groups were external genital pruritus (26-27%), genital burning (23-24%), headache (19-21%), genital irritation (15-16%), genital discharge (3-7%), and respiratory congestion (3-5%). See Table 11a above. When classified by body system, the majority of adverse experiences noted occurred in the genital/reproductive body system. Adverse experiences by body system that occurred at frequencies of >10% are summarized in Table 11b above. For a listing of the ADEs noted which occurred at frequencies of 2-5%, please see Appendix I.

Differences in the incidence of adverse experiences between treatment groups were tested for statistical significance by sponsor for the following, without reaching statistical significance:

- patients reporting at least one adverse experience
- any body system with at least a 10% incidence in any treatment group
- any individual adverse experience with at least a 5% incidence in either treatment group
- combined genital/reproductive adverse experiences of specific interest.

No deaths were reported in study 95-005-P, and IND safety reports were filed for the following 2 patients:

- Patient #19006 in M3C group: 34 y.o. female, hospitalized for severe depression for 2 weeks beginning the day of study admission. Patient had a history of depression; no study medication was taken, and the case is considered not drug-related.

- Patient #26001 in M7C group: 40 y.o. female, hospitalized for 2 days for severe chest pain, dizziness, nausea and vomiting. M.I. was ruled out. Patient also had a history of concurrent anemia and was placed on ferrous sulfate and folic acid. This case was not considered drug-related.

Finally, there were no findings on follow-up gynecologic examinations that suggested drug toxicity in both treatment groups. One patient in the MONISTAT 7 group was found to have old solidified medication high in the vagina at the first follow-up visit.

Study 95-007-P

Study protocol was very similar to the protocol for Study 95-005-P. Four hundred and twenty nine patients with VVC were entered into this study. Three drug regimens were studied but only the results from two treatment groups will be presented. (The third group of patients were given miconazole nitrate 2.8%.) A total of 284 patients were assigned to the 2 treatment groups under consideration (MONISTAT 7 and MONISTAT 3) and 276 were evaluable for safety. Compliance was assessed as 94% (131/139) in the M3C group and 95% (130/137) in the M7C group. Three patients (1 M3C and 2 M7C) who did not use study medication, and 5 patients (2 M3C and 3 M7C) who were lost to follow-up with no safety data were excluded from the safety analysis.

Table 12: Summary of Adverse Experiences in Study 95-007-P

	Miconazole Nitrate 4% (new)		MONISTAT 7 (old)	
	%	N=139	%	N=137
Any adverse experience	65%	91	64%	87
D/C drug 2° ADE		6		1
Severity of ADE	%	N=269 events	%	N=281 events
Mild	36%	97	36%	100
Moderate	36%	96	45%	125
Severe	28%	76	20%	56
Relationship to Drug	%	N=269 events	%	N=281 events
Not related	35%	94	36%	100
Unlikely related	20%	53	25%	68
Possibly related	32%	87	32%	91
Probably related	9%	24	6%	17
Highly probably related	9%	25	2%	5

Sixty-five percent of women in the 4% miconazole nitrate group (M3C) experienced a total of 270 adverse experiences while 64% in the MONISTAT 7 group (M7C) experienced 281 adverse experiences. In the M3C group, 28% of ADEs were considered severe. Among these severe cases, 56/76 were vulvovaginal in nature, such

as pain, irritation, burning or pruritus of the female genitalia. In the M7C group, 20% of the ADEs were considered severe. Among these severe cases, 31/56 cases were vulvovaginal in nature. A classification of the relationship of the ADE to the study drug is also summarized in the Table 12 above.

Medical Officer's Comments:

The sponsor's tabulation of ADEs in Table 12 above show similarity in number of ADE experiences between the M3C and M7C groups. There is one line item where there appears to be a higher frequency of ADEs in the M3C group, i.e. ADEs classified as highly probably related to drug; 9% (M3C) vs. 2.5% (M7C). Further examination of these adverse events in the databases (MED95007 and 9507DATA) provided by sponsor revealed that the actual descriptions of the ADEs in both treatment groups did not appear to be different. All ADEs were vulvovaginal (VV) in nature (such as VV itching, irritation, or burning). By MO calculations, the difference in frequency of ADEs that were considered highly probably related between M3C and M7C is significant. Since each subject could report more than one ADE, when each mention of ADEs were linked to individual patients, the difference (by number of subjects affected) between the M3C and M7C groups persisted, and remained significant. See Table 13 below.

Table 13: ADEs that are Probably Related or Highly Probably Related to Drug

	Miconazole Nitrate 4%		MONISTAT 7		By MO: (M3C-M7C)
By Subject:	N=139 subjects		N=137 subjects		Difference % (95% CI)
Relationship to Drug	%	N	%	N	
Highly probably related	9.4%	13	2.2%	3	[redacted]
By Event:	N=269 events		N=281 events		[redacted]
Relationship to Drug	%	N	%	N	
Highly probably related	9%	25	2.5%	7	[redacted]

Among all severe ADEs, there were 52/76 cases (68%) cases in the M3C group which were noted to be possibly, probably, or highly probably related to the drug. Only one patient, #5102 (vulvovaginal burning, itching, irritation, and vulvar excoriation) had an outcome coded as ongoing, although, under action required for the ADE, no action was required. Patient #2906 (redness around urethra) and Patient #3904 (vulvovaginal irritation) had outcomes coded as being still under treatment. However Patient #2906 received no action while Patient #3904 received counteractive medication. All of the other patients with severe ADEs with any likelihood of drug-relatedness recovered from the event. No one in this group was hospitalized. Study drug was discontinued in 6 patients and all 6 patients recovered.

A similar analysis of the patients in the M7C group follows:
Among all severe ADEs noted in the M7C group, 35/56 cases (63%) were thought to be possibly, probably, or highly probably related to the drug. Only 3 patients, #1805 (vulvovaginal itching, irritation, and burning), #3305 (vaginal discharge), and #9101 (vaginal irritation and burning) had outcomes coded as ongoing, although, under action

required for the ADE, no action was required. All of the other patients with severe ADEs with any likelihood of drug-relatedness recovered from the event. No one in this group was hospitalized. Study drug was not discontinued in any patients in this group; i.e. patients with severe ADEs thought to be related to drug in any way.

A total of 7 patients discontinued study medication. The information for discontinuing drug in these 7 patients are provided in Table 14 below, along with a classification of drug-relatedness. In the 6 patients on miconazole nitrate 4%, it was thought that the adverse experience was highly probably related to the study drug in 4 of them (Patients: #08003, #08903, #00605, #06504) and possibly related in the other 2 (Patients: #03701, #02804). All of the ADEs in these 7 patients were classified as severe, with study drug being discontinued prior to completion of full course, except in Patient #03701 in M3C group who received 4 doses. All 6 of the patients on M3C recovered, while the 1 patient on M7C was treated with fluconazole, which leads one to surmise that the ADE may be more related to the underlying disease and not to the drug.

Table 14: Drug Discontinuations in Study 95-007-P

Study Drug	Patient	Age/ Race	ADE	Severity/ Relation	Action	Outcome	Other Notes
M3C	#08003	26/C	vulvovaginal burning & itching	severe/ highly probable and possible	study drug d/c after 1 dose	recovered	also receiving other systemic medications
M3C	#03701	19/C	vaginal burning & itching on insertion	severe/ possible	study drug d/c after 4 doses	recovered	
M3C	#08903	18/C	vaginal burning & irritation	severe/ highly probable	study drug d/c after 1 dose	recovered	
M3C	#00605	44/C	increased vaginal burning	severe/ highly probable	study drug d/c after 1 dose	recovered	has sarcoidosis
M3C	#06504	25/C	vaginal burning & itching	severe/ highly probable	study drug d/c after 2 doses	recovered	
M3C	#02804	26/C	vaginal itching & irritation & uterine pain	severe/ possible	study drug d/c after 2 doses	recovered	
M7C	#01805	56/C	vulvovaginal itching and irritation	severe/ possible	none took all study medication	ongoing	treated with fluconazole

Table 15a: Most Frequently Reported Adverse Experiences by Primary Term (>5%)

Adverse Experiences	Treatment Group			
	Miconazole Nitrate 4% (N=139)		MONISTAT 7 (N=137)	
	N	%	N	%
Burning, female genitalia	36	26%	31	23%
Pruritus, external female genitalia	32	23%	32	23%
Irritation, female genitalia	29	21%	32	23%
Headache	25	18%	25	18%
Dysmenorrhea	8	6%	7	5%
Discharge, female genitalia	6	4%	8	6%
Pain, abdominal	7	5%	5	4%
Nausea	3	2%	9	7%
Upper respiratory infection	3	2%	8	6%

Table 15b: Body Systems with the Highest Incidence of Adverse Experiences (>10%)

	Miconazole Nitrate 4% (new)		MONISTAT 7 (old)	
Body System	%	N=139	%	N=137
Genital/reproductive system	47%	65	43%	59
Nervous system	19%	27	22%	30
Gastrointestinal system	11%	15	16%	22
Respiratory system	8.6%	12	14%	19

The most frequently reported ADEs (>5%) in both groups were genital burning (23-26%), external genital pruritus (23%), genital irritation (21-23%), headache (18%), dysmenorrhea (5-6%), genital discharge (4-6%), abdominal pain (4-5%), nausea (2-7%), and upper respiratory infection (2-6%). See Table 15a above. When classified by body system, the majority of adverse experiences noted occurred in the genital/reproductive body system. Adverse experiences by body system that occurred at frequencies of >10% are summarized in the above Table 15b. For a listing of the ADEs noted which occurred at frequencies of 2-5%, please see Appendix II.

Differences in the incidence of adverse experiences between treatment groups were tested for statistical significance for the following, without reaching statistical significance:

- patients reporting at least one adverse experience
- any body system with at least a 10% incidence in any treatment group
- any individual adverse experience with at least a 5% incidence in either treatment group
- combined genital/reproductive adverse experiences of specific interest.

No deaths were reported in study 95-007-P, and the one IND safety report filed was for the Patien.. #06602 in the miconazole nitrate 2.8% group. The case was considered not drug-related.

Finally, there were no findings on follow-up gynecologic examinations that suggested drug toxicity in both treatment groups. One patient in the MONISTAT 7 group had residual medication noted at the first follow-up visit.

Conclusions

There is extensive marketing experience, both Rx and OTC, with the active ingredient miconazole nitrate at doses ranging from 100 mg to 1200 mg, in various formulations including cream, suppository and ovule. The majority of adverse experiences reported are vulvovaginal in nature.

Given the concern about direct OTC marketing of this new cream formulation without prior experience with this formulation worldwide, it was pertinent to gather information from similar cream formulations already marketed, as well as from comparative trials comparing the new formulation to a currently marketed formulation. The comparative data between the 2% original cream formulation and TERAZOL cream (upon which this new cream formulation was based), and between the new cream formulation and the old cream formulation in MONISTAT 7 did not any adverse experiences associated specifically with this new cream formulation of miconazole. Further, the adverse event reports are not substantially different from what is known and observed with similar marketed products. However, the caveat is that much of this data is limited in number and scant in detail.

The best information about MONISTAT 4% vaginal cream in the new formulation is derived from the clinical trials 95-005 and 95-007. One should note that in both clinical trials, there were more patients with ADEs thought to be severe and related in some way to the drug. However, these numbers are too small to allow any definitive conclusions that the new MONISTAT 4% vaginal cream is indeed different from the old MONISTAT 7 vaginal cream. While there is a suggestion of drug-relatedness in the clinical trials, especially in Study 95-007-P, of the more frequent occurrences of vulvovaginal burning, itching, irritation, etc., it is also likely that these symptoms reflect the condition itself (vulvovaginal candidiasis) for which drug treatment is sought. One could also postulate that the higher concentration of active ingredient in the 3-day cream may indeed be more irritating to the vaginal mucosa. Given the newness of this specific MONISTAT formulation, post-marketing surveillance activities should actively and carefully monitor for frequent and any unexpected adverse experiences.

In conclusion, the body of knowledge presented for this product, including the comparative trials with prior approved and newer formulation modifications, the worldwide postmarketing experience of miconazole nitrate products, provides reasonable assurances that the safety of miconazole nitrate 4% in the new cream formulation is comparable to that of currently marketed miconazole products for vulvovaginal candidiasis. Thus, there are no new safety concerns to prevent approval

of this product. However, given that this is a direct to OTC formulation, Phase IV postmarketing surveillance requirements must be strictly complied with.

/S/ 3/24/98

Ling Chin, M.D., M.P.H.
DOTCDP

/S/ (acting)

Linda M. Katz, M.D., M.P.H.
Deputy Director, 3/24/98
DOTCDP

APPEARS THIS WAY
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Reviewer:	Ling Chin, M.D., M.P.H.
Division:	OTC Drug Products, HFD-560
NDA #:	20-827
Drug:	Monistat 3 Vaginal Cream (miconazole nitrate 4%)
Sponsor:	Advanced Care Products
Date Submitted:	July 17, 1997
Date Received:	July 23, 1997
Date Completed:	August 12, 1997

Additional MO Comments:

. These comments are provided in addition to comments already stated above by Dr. Lechter.

1) Methodology:

There is no description of the population to be targeted by this label comprehension study. It is customary in label comprehension studies to target consumers who intend to use the product under study at some time in the near future. While not exactly reaching the consumer at the point of purchase, it may approximate those consumers who have the intention of trying to select a product from the vaginal anti-fungal shelf. It would therefore be important to recruit women who think they have a vaginal yeast infection and are interested in using an OTC vaginal antifungal product.

The sponsor stated that consumers will be recruited from shopping malls in 20 geographically dispersed malls in the contiguous U.S. It is unclear if this method of recruitment will result in a demographically representative group of women who will use an OTC vaginal antifungal product, especially women of lower literacy and educational levels.

This label comprehension study would be a much more rigourous study if a control group is included in the study design. It would be appropriate to consider the current version of the Monistat OTC label as the control label vs. a proposed Monistat OTC Drug Facts format label. The sponsor should be reminded that FDA has announced its intention to standardize all OTC drug labels (Federal Register/Vol. 62, No. 39/February 27, 1997).

2) Analysis Plan:

Communication objectives were not specified by the sponsor. Despite the amount of information provided by the carton label and the package insert; there are key communication objectives that must be conveyed to the consumer so that the consumer can self-select and use appropriately without benefit of a learned intermediary. For example, key communication objectives as regards this product should include the following:

- what is the intended use of the product
- who should use the product
- who should not use the product
- when to consult a doctor
- differentiation between the 1-day and 7-day vaginal antifungal products, such as expectation of benefit (cure) and expectation of symptom relief.

There is other information which would be important to the overall use of the product, but which may not be as critical. It would also be important to establish communication objectives for all such information deemed important.

Once communication objectives are specified, then questions can be designed to address the objectives directly. The analysis plan should state which objective would be addressed by which questions. Where the specific objective is addressed by more than one question, the analysis plan should state how that objective would be satisfied by the questions; e.g. the objective is satisfied only if all questions are answered correctly, or if 2 out of 3 questions are answered correctly, etc.

3) Questionnaire:

There were no questions on the questionnaire that asked about the subjects' pertinent medical history. Some medical information may be warranted. For example questions pertaining to whether or not the subjects had had previous vaginal infections, what types of vaginal infections, had a doctor diagnosed their vaginal yeast infection before, frequency of vaginal yeast infections, last episode of vaginal yeast infection, etc., may elicit information that would provide corroboration of whether or not the subjects made the appropriate decision based on the labeling.

Most of the questions are a test of comprehension but may not demonstrate subjects' intention with regard to themselves. It would be important to include questions that specifically ask the subjects what they would do if they were the ones using the product. It would be preferable to use different types of questions such as open-ended/closed-ended questions, scenarios, or questions that relate to the subject directly to test the concepts of:

(a) self selection:
- what the product can be used for
- who can use, who should not use

(b) appropriate use:
- how to use, e.g. duration, administration
- when to check with a doctor

(c) expectation of benefit:
- when to expect relief

- 1 day vs. 3 day vs. 7 day products.

Questions should not be leading, and objective questions should include correct and incorrect items in no specific patterns.

Apart from the questions that are deemed essential for appropriate self-selection and proper use (i.e. key communication objectives), questions should also be included that would demonstrate the consumer's level of comprehension of other information provided by the carton label and package insert.

4) Label:

A Monistat label in the OTC Drug Facts format should be developed. The agency would be willing to work with the sponsor in developing such a label.

5) Recommendations:

i) Revise protocol to include a comparator group.
ii) State the communication objectives; designate which objectives are key
iii) Submit an analysis plan.
iv) Ensure inclusion of subjects with low literacy levels.
v) Revise the questionnaire to include essential medical information about the subject, some open-ended questions, questions based on scenarios. Questions about all important aspects of the labeling should be included.
vi) Develop a Drug Facts format Monsitat label.
vii) Submit the full label for review prior to initiation of the trial.

/S/ 9/5/97

Ling Chin, M.D., M.P.H.
Medical Officer
DODP

/S/

Linda M. Katz, M.D., M.P.H.
Deputy Director
DODP

cc:
HFD-560
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HFD-590

HFD-590
C. Chi

Reviewer:	Ling Chin, M.D., M.P.H.
Division:	OTC Drug Products, HFD-560
NDA #:	20-827 General Correspondence
Drug:	Monistat 3 Vaginal Cream (miconazole nitrate 4%)
Sponsor:	Advanced Care Products
Date Submitted:	November 17, 1997
Date Received:	November 28, 1997
Date Completed:	January 9, 1998

Additional MO Comments:

These comments are provided in addition to comments already stated in Dr. Lechter's review. This submission contained sponsor's response to the joint reviews provided by DDMAC, DOTCDP, and DSPIDP. The sponsor also submitted a revised protocol and questionnaire.

1) Design and Methodology:

Since the final rule regarding OTC labeling is being developed, and all OTC labeling are expected to be in compliance, it is no longer necessary to test a Drug Facts format label vs. a label in the old format. Thus, the comparator label group need not be included in this label comprehension study.

The target population for this label comprehension study needs to be described further. Consumers who intend to use the product under study at some time in the near future are still the subjects targeted for participation in this study. This includes both the consumers who have had a vaginal yeast infection before and consumers who have not had a past episode of vulvo-vaginal candidiasis (VVC). Since we are most interested in the adequacy of the label in those who intend to use the product, it is important that we have substantial information on this group of consumers; therefore the 25% expected proportion of consumers who have ever had VVC in the study sample is inadequate. We would suggest that at least 50% of the study sample be consumers who have had an episode of VVC in the past.

Further the study sample should include a demographically balanced proportion of subjects by age, race, and educational levels. Since the label allows for use in females down to the age of 12 years, the study sample should include subjects younger than age 18. There should also be sufficient numbers of subjects of low literacy to ensure that information can be derived about this group.

2) Analysis Plan:

There is no predetermined cut-off for (in terms of % of correct responses) establishing that communication objectives are achieved. The nature of the information, i.e. how important it is for appropriate selection and use, determines if the label is adequate in conveying that specific information to the consumer. For key

communication objectives, it would be important that almost everyone gets the message. If the study results show that key messages are not being conveyed, then changes should be made to improve that message. For secondary communication objectives, the level of concern may not as critical, and therefore, the tolerance for incorrect responses may be broader.

The analysis plan should include an assessment of the percent of participants who were able to provide correct responses to key questions. The determination of whether participants answered correctly would be based on their responses to two questions. For example, to determine if a participant selected to use/not use the product appropriately, participants' responses to whether they would use/not use the product would be validated by their responses to the question of whether or not they had had a previous diagnosis of VVC from a doctor. Results can be tabulated in the following manner:

	Subject's Selection:	
Medical History:	Can Use Product	Can not Use Product
Had MD Dx of VVC	Correct	Incorrect
Did not have MD Dx of VVC	Incorrect	Correct

Wherever possible, such a tabulation should be made of the appropriateness of participants' responses to other questions by the information that is available on the participants' medical history and product use history.

3) Questionnaire:

Some medical information was added in this revised questionnaire. However, there should be a direct question about whether or not the subject has ever been diagnosed by a doctor as having a vaginal yeast infection. The question dealing with this topic is too indirect. There should also be a direct question to the subject asking if she can use this product if she thinks she has a vaginal yeast infection.

We also have several suggestions about the rewording of questions and simplifying the language. These comments have been consolidated and incorporated in Dr. Lechter's review under suggestions for the questionnaire.

A general comment about the revised questionnaire is that it is too long. Questions testing the same information on the educational brochure as the carton label should not be repeated. Only the additional information from the educational brochure that was not presented in the carton label should be tested.

4) Label:

A Monistat label in the OTC Drug Facts format should be used. The Agency is also developing class labeling for all OTC vaginal antifungal products. We will provide further guidance on class labeling at a later time.

5) Recommendations:

i) Appropriate to not have a comparator label
ii) Include higher proportion of subjects with VVC; at least 50%
iii) Include subjects with low literacy levels, enough to allow for analysis of this subset
iv) Incorporate questionnaire revisions; do not retest the same information for both the carton and the educational brochure; test only the additional information provided in the educational brochure
v) Carton label and educational leaflet should be as close to market versions as possible
vi) Submit the full color mock-up of the label for review prior to initiation of the trial.

/S/

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